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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/786,988	01/23/1997	DANIEL P. LITTLE	24736-2001D	5922

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EXAMINER	
GAKH, YELENA G	

ART UNIT	PAPER NUMBER
1743	

DATE MAILED: 04/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/786,988	LITTLE ET AL.	
	Examiner	Art Unit	
	Yelena G. Gakh, Ph.D.	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *108-146* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *108-146* is/are rejected.

7)☒ Claim(s) *144-145* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment filed on 02/21/05 is acknowledged. Claims 108-146 are pending in the application.

Response to Amendment

2. In response to the amendment rejections of claims 141-143 under 35 U.S.C. 112, first and second paragraphs are withdrawn.

Rejection of the pending claims is slightly modified in light of the Applicants' arguments.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 144 and 145 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Since it may be assumed that the spots formed on the substrate are circular, it is not clear, which two dimensions 450μm x 450μm or 800μm x 800μm are meant in defining the spot size. Moreover, the area of the spot would not be calculated as 450 x 450 μm^2, if 450μm is the spot diameter (D). It rather will be less than this product ($\pi/4D^2$).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. **Claims 108-118, 120-123, 125, 132-141 and 143-146** are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicola et al. (Rapid Commun. Mass Spectrom., 1995) in view of Li et al. (JACS, 1996, IDS) and Hayes et al. (US 5,658,802, IDS).

Nicola teaches "application of the fast-evaporation sample preparation method for improving quantification of angiotensin II by matrix-assisted laser desorption/ionization" with obtaining a substrate for MALDI analysis comprising an array of matrix spots. Nicola emphasis increased reproducibility of mass spectra from spot to spot obtained by depositing an array of 2.5-10 μL droplets of the matrix on the MALDI substrate, drying the spots and applying ~ 1.0 μL of analyte/matrix solution on top of the dried matrix spots. While Nicola further indicates that "this resulted in greater crystal thickness compared to previously published results, which we consider essential for improvement in signal reproducibility (as previously reported, much less matrix was used for the matrix crystal layer, resulting in a much thinner layer)" (page 1166, left column), Li emphasizes that very reproducible spectra and results are obtained from repeated preparations (page 11663, right column) comprising depositing 0.9 μL of matrix solution forming "a very thin matrix layer" (page 11663, left column). Li also indicates that "the idea of microspot MALDI is to reduce the sample presentation surface with respect to the laser desorption site

and ion acceptance volume in the mass spectrometer to improve the sample efficiency" (Li, page 11662, right column). Therefore, it would have been obvious for any person of ordinary skill in the art to further decrease volumes of MALDI matrix solutions deposited on the substrate compared to volumes used by Nicola for the reasons described by Li, i.e. "to reduce the sample presentation surface with respect to the laser desorption site and ion acceptance volume in the mass spectrometer".

While Nicola and Li do not specifically disclose disposing 0.2-20 nL of the matrix solution on the substrate, Hayes teaches "method and apparatus for making miniaturized diagnostic arrays" using electro-mechanical or piezoelectrical dispensers to place extremely small drops (10 pl to 1 nl) of fluid on substrates to form diagnostic arrays. Hayes indicates, "the invention thus provides a highly accurate, rapid and repeatable method of placing extremely small drops (10 pl to 1 nl) of fluid reagent on substrates to form diagnostic arrays. By using such small drops and accurately positioning them on the substrate, test strips can be formed which have a larger number of probes located within a smaller area than is achievable with prior methods" (col. 2, lines 49-55).

It would have been obvious for any person of ordinary skill in the art to modify Nicola's method by decreasing volumes of deposited matrix solution to 0.2-20 nL implying Hayes technique, because Li teaches microspot MALDI with highly reproducible results for picoliter amounts of the analyte when using very thin MALDI matrix spot formed on the probe wit an aim "to reduce the sample presentation surface with respect to the laser desorption site.

8. **Claims 108-118, 120-123, 125, 132-141 and 143-146** are rejected under 35 U.S.C. 103(a) as being unpatentable over Vestal (US 5,498,545, IDS) in view of Vorm et al. (Anal. Chem., 1994) and Hayes.

Vestal teaches an automated MALDI MS analysis for a plurality of samples, specifically DNA analytes, deposited as 100 nL droplets (col. 4, line 59) on a MALDI plate made of "stainless steel or other suitable electrically conducting material" (col. 3, lines 57-58). The samples are prepared as mixtures of the analytes with MALDI matrix.

Vestal fails to teach depositing MALDI matrix without the analyte and allowing the spot to dry before depositing the analyte.

Vorm teaches a "fast evaporation" method of MALDI matrix deposition on a MALDI plate, comprising depositing ~ 0.5 μL drop of the matrix (ferulic acid, sinapic acid, etc.) on the MALDI stainless steel probe tip and allowing the spot to dry before applying a droplet of an analyte, indicating

"improved resolution and very high sensitivity in MALDI TOF of matrix surfaces made by fast evaporation" (Title). "In the new procedure, matrix solution is applied to the probe tip of the mass spectrometer in a highly volatile solvent, e.g., acetone, to obtain very fast evaporation of the solvent. This leads to the formation of a dense, flat, and thin film presumably consisting of very small crystals of matrix. A small volume of analyte solution is then placed on top of the matrix surface, and the liquid is allowed to evaporate slowly. The only constraint on the analyte solution is that it must not completely re-dissolve the matrix surface, but only the outermost layer. We speculate that this layer is then doped with analyte molecules" (page 3282, left column). The solvents are acetone, acenotrile, methoanol, acetic acid and trifluoroacetic acid (page 3282). Moreover, Vorm specifically indicates, "the above procedure applies to large and flat probe tips. In systems which use small or curved probe tips slight alternations may be necessary to achieve homogeneous matrix surfaces. *The amount of matrix solution and its concentration can be used to adapt the procedure to the system used*" (page 3283, left column).

It would have been obvious for any person of ordinary skill in the art to modify Vestal's method of MALDI MS analysis by Vorm's method of depositing MALDI matrix as a droplet and allowing it to dry before depositing the analyte, because Vorm specifically indicates that it improves resolution and provides very high sensitivity in MALDI TOF analysis.

While Vestal and Vorm do not teach depositing drops of 0.2-20 nL, Hayes teaches "method and apparatus for making miniaturized diagnostic arrays" using electro-mechanical or piezoelectrical dispensers to place extremely small drops (10 pl to 1 nl) of fluid on substrates to form diagnostic arrays. Hayes indicates, "the invention thus provides a highly accurate, rapid and repeatable method of placing extremely small drops (10 pl to 1 nl) of fluid reagent on substrates to form diagnostic arrays. By using such small drops and accurately positioning them on the substrate, test strips can be formed which have a larger number of probes located within a smaller area than is achievable with prior methods" (col. 2, lines 49-55). Different electro-mechanical dispensers comprising vesicles with chambers and transducers are disclosed in col. 2.

It would have been obvious for any person of ordinary skill in the art to modify Vestal-Vorm's MALDI MS analysis, including analysis of DNA by using Hayes' method of depositing very small droplets (less than 1 nL) of the matrix material because, as Hayes indicated, it allows creating a plurality of highly reproducible and volume-controlled spots, which is essential for obtaining reproducible MALDI spectra, the importance of which is well recognized in the art and because Vorm teaches that

depositing small volumes of matrix solution in highly volatile solvents lead to formation of a dense, flat and thin film of very small crystals of matrix, which provide reproducible results for MALDI analysis.

9. **Claims 119, 124, 126-131** are rejected under 35 U.S.C. 103 (a) as being unpatentable over Nicola in view of Li and Hayes or over Vestal in view of Vorm and Hayes, as applied to claims 108-118, 120-123, 125, 132-141 and 143-146 above, and further in view of Hancock et al. (US 5,716,825, IDS).

Nicola in view of Li and Hayes or Vestal in view of Vorm and Hayes do not specifically disclose other matrices, or materials of the substrate other than steel.

Hancock discloses an integrated nucleic acid analysis system for MALDI-TOF MS, and describes in particular a thin film sample support, which is a substantially "planar manifold made of a non-conducting material that includes a microchannel and other necessary components of a miniturized sample preparation compartment, an interface to non-consumable parts, and an ionization surface for MALDI-TOF MS. Such a miniaturized device may be formed from a variety of materials (e. g., **silicon, glass, low cost polymers**) by techniques that are well known in the art (e.g., micromachining, chemical etching, laser ablation, and the like)" (col. 4,11. 34-44). Hancock further describes a process wherein analyte is embedded in a solid or crystalline "matrix" of light-absorbing molecules (e. g., **nicotinic, sinapinic, or 3-hydroxypicolinic acid**) (col. 6,11. 15-25). Hydrophobic and hydrophilic MALDI ionization surfaces, such as metals (**gold, copper, stainless steel**), glass, silica, nylon and other synthetic polymers, agarose and other carbohydrate polymers, and plastics are disclosed as surfaces for actively capturing analyte (col. 6,11. 38-44). Other capture regions are disclosed, such as **surface of a bead, particle** or planar support treated with a bifunctional cross-linking reagent. "According to the practice of the present invention, a capture region may be formed in any microstructure surface in the sample preparation compartment by linking an analyte binding partner directly to the surface, and on MALDI ionization surfaces integrated with the preparation compartment. Alternatively, a capture region may be formed on the surfaces of beads, which can be chemically attached to the surface of the support, or magnetically attached by using magnetically responsive beads and applying a magnetic field to anchor the beads to the desired region of the support. Magnetically responsive beads and particles are well-known in the art and are commercially available from, for example, Dynal. RTM., Inc. (Lake Success, N.Y.) and Bangs Laboratories, Inc. (Carmel, Ind.)" (col. 7, 11. 30-43).

It would have been obvious at the time the invention was made to a person having ordinary skill in the art to use any of the materials described by Hancock in Nicola-Li-Hayes' or Vestal-Vorm-Hayes' methods, because Hancock discloses them as suitable materials for performing MALDI-MS analysis of biological materials, specifically DNA.

Response to Arguments

10. Applicant's arguments filed 02/25/05 have been fully considered but they are not fully persuasive.

Regarding rejection over Vestal, Vorm and Hayes, the examiner failed to find any teaching away of using smaller volumes of matrix solution deposited on the MALDI substrate in Vorm's reference. The examiner has to admit that the recitation from Vorm's reference regarding the size of the crystals produced from matrix solution provided by the Applicants is ambiguous. However, since Vorm explicitly indicates that in his method "a dense, flat, and thin film presumably consisting of **very small crystals of matrix**" is formed, the statement that "the surface area of crystals should be very large" (page 3285) may refer to the total surface area of small crystals of MALDI matrix, rather than the large surface area of a single crystal. It is quite obvious that the dense, flat and thin film of small crystals can provide large crystal surface area, which is more homogenous, than the total surface area of a few large crystals. The examiner interprets Vorm's statement on page 3285 exactly this way. If the Applicants are of a different opinion on what Vorm discloses, the examiner would appreciate, if they provide their own interpretation of Vorm's disclosure. At this point, the examiner does not see any teaching away from using even smaller volumes than disclosed by Vorm in his paper. Moreover, his statement that concentration and volume of matrix solution are variables, which can be adjusted depending on the system and probe used, directly lead any routineer in the art to optimization of these parameters. The Applicants' assumption that any person of ordinary skill in MALDI spectrometry would still apply 0.5 μl or 0.3 μl of the analyte to the spots that are 10-100 times less than those disclosed by Vorm is at least unjustified.

Combination of Nicola and Hayes is modified in view of the Applicants' arguments. The examiner would like to notice, however, that the recitation from Nicola's reference related to the

thickness of the spot specifically indicates that "much less matrix was used", not that "smaller volume of matrix solution" was used. It is possible to use very small volumes of a matrix solution and still get thick spots, if the solution is concentrated. Therefore, the examiner does not consider Nicola's statement "teaching away" from using smaller *volumes* of matrix solutions. However, since this issue is raised by the Applicants, the examiner uses additional reference by Li, who indicates that "very thin matrix films" obtained after evaporation of the solvent yield highly reproducible MALDI spectra. It may be concluded therefore, that the origin of Nicola's results is different from what he assumed regarding the thickness of the matrix layer.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

YELENA GAKH
PRIMARY EXAMINER

4/12/05